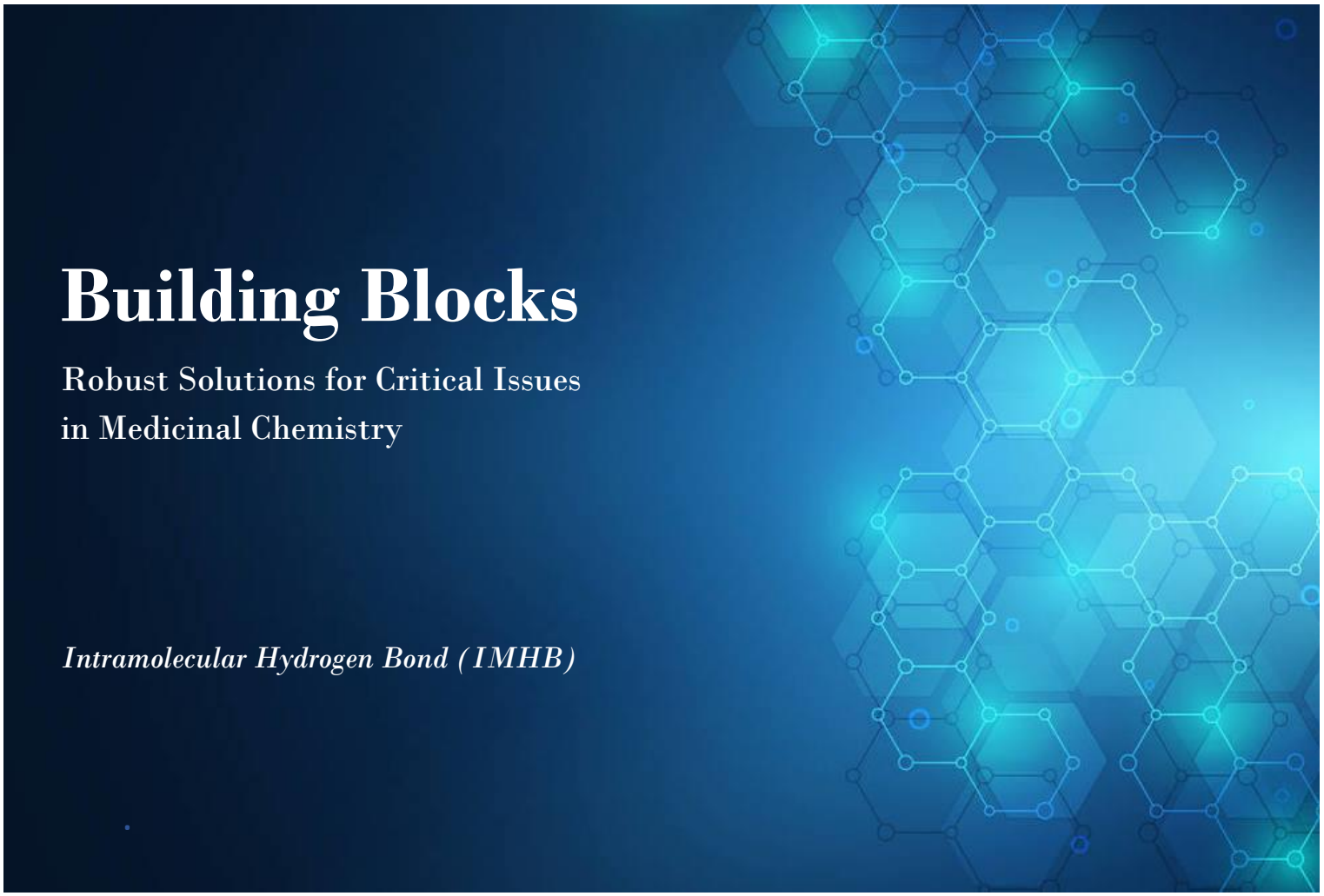
Building Blocks
Robust Solutions for Critical Issues
in Medicinal Chemistry
Intramolecular Hydrogen Bond (IMHB)

Intramolecular Hydrogen Bond (IMHB) in Medicinal Chemistry

The formation of intramolecular hydrogen bonds has a very pronounced effect on molecular structure and properties. [1] Medicinal chemists widely employ IMHB strategy to modify molecules with respect to locking conformation, increasing permeability, aqueous solubility, scaffold hopping, etc. In the circumstances, building blocks bearing HBD or HBA to form IMHB are of great value in drug discovery.

As shown in **Figure 1**, scaffolds 1,5-naphthyridine in compound **3** and pyrazolo[1,5-a]pyrimidine in compound **4**, which have nitrogen atoms highlighted in red color forming IMHB with adjacent hydrogen atoms highlighted in blue color, decreased efflux ratio significantly comparing with compound **1** and compound **2**. [2] Quick access of dichloro building blocks listed in the right of **Figure 1** as starting material for paralleled medicinal chemistry, enabled the structure-property relationship (SPR) study efficiently.

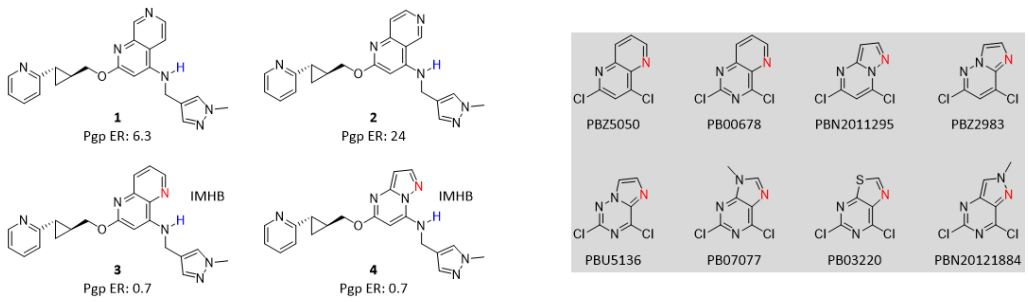

Figure 1. 1,5-Naphthyridine in compound **3** and pyrazolo[1,5-a]pyrimidine in compound **4** decreased efflux ratio.

A fluorine atom ortho- to the NH of an anilide can influence conformation. Biological evaluation of isomers **5** and **6** demonstrated a 10-fold difference in CGPR affinity, with F-HN interaction favoring desired binding conformation (**Figure 2**). [3]

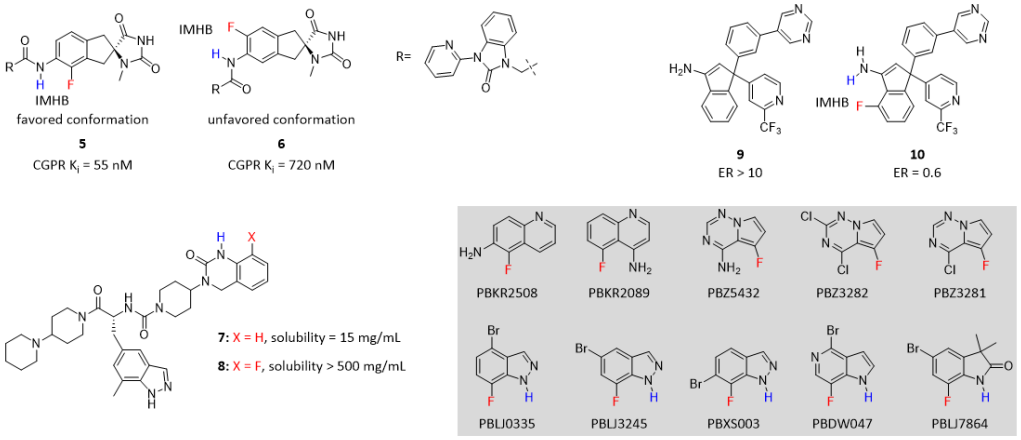

Figure 2. IMHB between F and N-H can influence many properties of molecule.

Replacing a hydrogen atom ortho- to an anilide N-H in compound **7** by a fluorine atom in compound **8** increased water solubility by 30-fold, probably due to “mask effect” of F on N-H. A positive effect on permeability was observed when comparing compound **9** and **10**, attributed to a weak interaction between F and one of N-H that reduces the number of HBD available to the

environment. Building blocks with F able to form IMHB with adjacent N-H as exemplified in **Figure 2**, are extremely useful and have been widely utilized in medicinal chemistry to improve molecular properties. [3]

Compound **11** was discovered as a potent GSK-3β inhibitor. However, cleavage of the cyclopropyl carboxamide group was observed in mouse serum. In co-crystal structure of **11** complexed with GSK-3β, a water-bridging hydrogen bond between the carbonyl of amide and the upper amide NH was observed, which may help to predispose the molecule to energetically favor the bioactive conformation (**Figure 3**). [4] With this in mind, the imidazo[1,2-b]pyridazine ring system appeared to be an attractive heterocyclic scaffold, with an interaction between amide NH (blue) and imidazole nitrogen atom (red) locking molecule in the desired bioactive conformation. When carboxylic acid building blocks, which have adjacent HBA to –COOH group, are converted to amide, IMHB are formed.

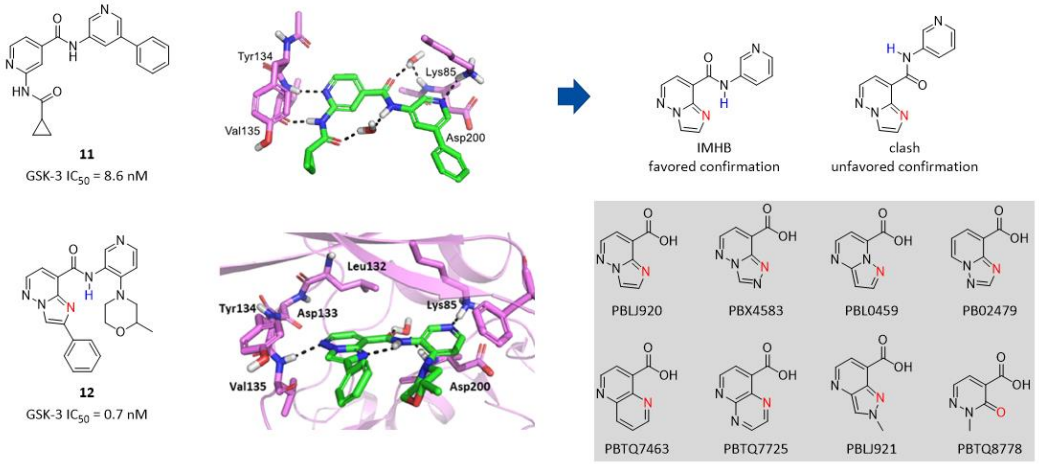

Figure 3. An interaction between amide N-H and imidazole N locks the molecule in the bioactive conformation.

References

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[4] Richard A. Hartz; *et al.* Design, structure-activity relationships, and in vivo evaluation of potent and brain-penetrant imidazo[1,2-b]pyridazines as glycogen synthase kinase-3beta inhibitors. *J. Med. Chem.* **2023**, doi:10.1021/acs.jmedchem.3c00133.

July. 2024

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